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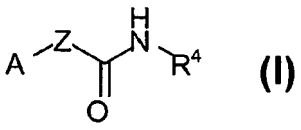
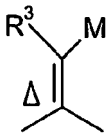
(54) Title: HETEROARYL COMPOUNDS



(I)



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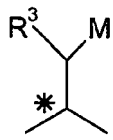

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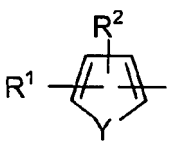
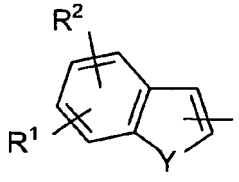


(IV)

or



(V)

(57) Abstract: According to the present invention there is provided a compound of formula (I) wherein Z isR3 is lower alkyl or halo lower alkyl having from 2 to 6 carbon atoms or arylalkyl or -(CH2)s-V where V is a 3 to 8-membered ring which is cycloalkyl, cycloalkenyl, or heterocycloalkyl having one heteroatom selected from oxygen and sulfur ; s is independently 0, 1 or 2; M is hydrogen or halo or lower alkyl or perfluoro-lower alkyl;A is or where Y is oxygen or sulfur, and its pharmaceutically acceptable salts thereof. These compounds are considered to be useful for the treatment of type II Diabetes.

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

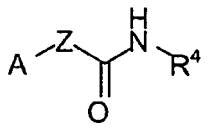
HETEROARYL COMPOUNDS

Glucokinase (GK, Hexokinase IV) is one of four hexokinases that are found in mammals [Colowick, S.P., in *The Enzymes*, Vol. 9 (P. Boyer, ed.) Academic Press, New York, NY, pages 1-48, 1973]. The hexokinases catalyze the first step in the metabolism of glucose, i.e., the conversion of glucose to glucose-6-phosphate, Glucokinase has a limited cellular distribution, being found principally in pancreatic beta-cells and hepatocytes. In addition, GK is a rate-controlling enzyme for glucose metabolism in these two cell types that are known to play critical roles in whole-body glucose homeostasis [Chipkin, S.R., Kelly, K.L., and Ruderman, N.B. in *Joslin's Diabetes* (C.R. Khan and G.C. Wier, eds.), Lea and Febiger, Philadelphia, PA, pages 97-115, 1994]. The concentration of glucose at which GK demonstrates half-maximal activity is approximately 8 mM. The other three hexokinases are saturated with glucose at much lower concentrations (<1 mM). Therefore, the flux of glucose through the GK pathway rises as the concentration of glucose in the blood increases from fasting (5 mM) to postprandial (≈10-15 mM) levels following a carbohydrate-containing meal [Printz, R.G., Magnuson, M.A., and Granner, D.K. in *Ann. Rev. Nutrition* Vol. 13 (R.E. Olson, D.M. Bier, and D.B. McCormick, eds.), Annual Review, Inc., Palo Alto, CA, pages 463-496, 1993]. These findings contributed over a decade ago to the hypothesis that GK functions as a glucose sensor in beta-cells and hepatocytes (Meglasson, M.D. and Matschinsky, F.M. *Amer. J. Physiol.* 246, El-E13, 1984). In recent years, studies in transgenic animals have confirmed that GK plays a critical role in whole-body glucose homeostasis. Animals that do not express GK die within days of birth with severe diabetes while animals overexpressing GK have improved glucose tolerance (Grupe, A., Hultgren, B., Ryan, A. et al., *Cell* 83, 69-78, 1995; Ferrie, T., Riu, E., Bosch, F. et al., *FASEB J.*, 10, 1213-1218, 1996). An increase in glucose exposure is coupled through GK in beta-cells to increased insulin secretion and in hepatocytes to increased glycogen deposition.

The finding that type II maturity-onset diabetes of the young (MODY-2) is caused by loss of function mutations in the GK gene suggests that GK also functions as a glucose sensor in humans (Liang, Y., Kesavan, P., Wang, L. et al., *Biochem. J.* 309, 167-173, 1995). Additional evidence supporting an important role for GK in the regulation of glucose metabolism in humans was provided by the identification of patients that express

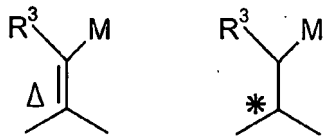
a mutant form of GK with increased enzymatic activity. These patients exhibit a fasting hypoglycemia associated with an inappropriately elevated level of plasma insulin (Glaser, B., Kesavan, P., Heyman, M. et al., New *England J. Med.* 338, 226-230, 1998). While mutations of the GK gene are not found in the majority of patients with type II diabetes, compounds that activate GK and, thereby, increase the sensitivity of the GK sensor system will still be useful in the treatment of the hyperglycemia characteristic of all type II diabetes. Glucokinase activators will increase the flux of glucose metabolism in beta-cells and hepatocytes, which will be coupled to increased insulin secretion and increased glucose utilization and glycogen synthesis. Such agents would be useful for treating type II diabetes.

According to the present invention there is provided compounds of formula (I):



(I)

wherein Z is

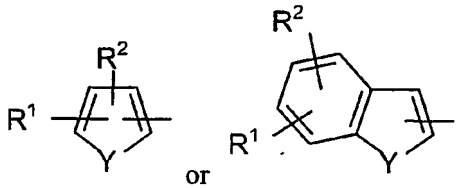


R^3 is lower alkyl or halo lower alkyl having from 2 to 6 carbon atoms or arylalkyl or –(CH_2)s-V where V is a 3 to 8-membered ring which is cycloalkyl, cycloalkenyl, or heterocycloalkyl having one heteroatom selected from oxygen and sulfur;

s is independently 0, 1 or 2;

M is hydrogen or halo or lower alkyl or perfluoro-lower alkyl;

A is



or

where Y is oxygen or sulfur, and

R^1 and R^2 are independently hydrogen, halo, amino, hydroxyamino, nitro, cyano, sulfonamido, lower alkyl, $-OR^5$, $-COOR^5$, perfluoro- lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl,

R^5 is hydrogen, lower alkyl or perfluoro-lower alkyl; or furthermore

R^2 can be $-(CH_2)n-NR^6R^7$, with n=1,2,3 or 4, and

R^6 and R^7 are independently hydrogen or lower alkyl; or together with the nitrogen atom to which they are attached form a five or six-membered heteroaromatic ring containing from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen; or a saturated 5- or 6-membered cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen; or

R^2 can be alkinyl, substituted with hydrogen, lower alkyl, hydroxy lower alkyl, lower alkoxy lower alkyl, an unsubstituted or hydroxy substituted cycloalkyl ring containing 5 or 6 carbon atoms, a five- or six-membered saturated heterocyclic ring which contains from 1 to 3 hetero atoms selected from the group consisting of sulfur, oxygen or nitrogen, or an unsubstituted five- or six-membered heteroaromatic ring, connected by a ring carbon atom, which contains from to 3 heteroatoms in the ring selected from the group consisting of sulfur, nitrogen and oxygen, or $-(CH_2)n-NR^8R^9$, with n=1,2, and

R^8 and R^9 are independently hydrogen or lower alkyl; or together with the nitrogen atom to which they are attached form a five or six-membered heteroaromatic ring containing from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen; or a saturated 5- or 6-membered cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen; or

R^2 can be $R^{10}-[(CH_2)y-W]z-$, with

W is oxygen, sulfur, -SO-, $-SO_2-$, and

R^{10} is a heteroaromatic ring, connected by a ring carbon atom, which contains from 5 to 6 ring members with from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur or nitrogen, or

aryl containing 6 or 10 ring carbon atoms, or

aryl containing 6 ring carbon atoms fused with a heteroaromatic ring containing 5 or 6 ring members with 1 or 2 heteroatoms in the ring being selected from the group consisting of nitrogen, oxygen or sulfur, or

a saturated 5- or 6-membered cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, or

a cycloalkyl ring having 5 or 6 carbon atoms, or

$-NR^{11}R^{12}$, with R^{11} and R^{12} being independently hydrogen or lower alkyl;

y is independently 0,1,2,3 or 4; z is independently 0,1; or

R^2 can be $R^{13}-(CH_2)t-U-$, with

U is -NHCO-, -CONH, $-NHSO_2-$, $-SO_2NH-$ and

R^{13} in the same meaning of R^{10} and

perfluoro-lower alkyl, lower alkyl, lower alkoxycarbonyl or

$-NR^{14}R^{15}$, R^{14} and R^{15} are independently hydrogen or lower alkyl; or together with the nitrogen atom to which they are attached form a five or six-membered heteroaromatic ring containing from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen; or a saturated 5- or 6- membered heterocycloalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen;

t is an integer being 0, 1, 2, 3 or 4;

R^4 is $-C(O)NHR^{16}$, or is R^{17};

R^{16} is hydrogen, lower alkyl, lower alkenyl, hydroxy lower alkyl,

$-(CH_2)n-COOR^{18}$, $-CO-(CH_2)n-COOR^{19}$;

R^{17} is an unsubstituted, mono- or di-substituted five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amide group shown, which five- or six-membered heteroaromatic ring contains from 1 to 4 heteroatoms selected from sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent to the connecting ring carbon atom; said mono- or di-substituted heteroaromatic ring being mono- or di-substituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, halo, nitro, cyano, $-(CH_2)n-OR^{20}$, $-(CH_2)n-COOR^{21}$,

$-(CH_2)n-CONHR^{22}$, $-(CH_2)n-NHR^{23}$,

n is 0, 1, 2, 3 or 4;

R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are independently hydrogen or lower alkyl,

and its pharmaceutically acceptable salts thereof.

The compounds of formula I have been found to activate glucokinase *in vitro*. Preferably the compounds of formula I have an enhanced solubility profile and further, have improved metabolic stability over the compounds of the prior art. They are particularly useful for increasing insulin secretion in the treatment of type II diabetes.

The present invention provides pharmaceutical compositions comprising a compound of formula I, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

Further, the present invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof for use as a pharmaceutical; and a compound of formula I, or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of type II diabetes.

The present invention also provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of disorders associated with GK dysfunction in mammals; the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of of type II diabetes.

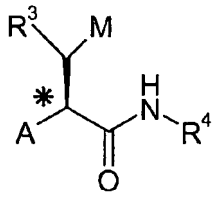
The present invention further relates to processes for the preparation of the compounds of formula I, or pharmaceutically acceptable salts thereof. In addition, the present invention relates to a method for the prophylactic or therapeutic treatment of type II diabetes, which method comprises administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof; to a human being or an animal in need thereof.

The present invention includes the pharmaceutically acceptable salts of the compounds of formula I. As used herein, the term "pharmaceutically acceptable salts" include acid addition salts, including salts formed with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic or organic sulphonic acids, for example, acetoxybenzoic, citric, glycolic, *o*- mandelic-l, mandelic-dl, mandelic d, maleic, mesotartaric monohydrate, hydroxymaleic, fumaric, lactobionic, malic, methanesulphonic, napsylic, naphthalenedisulfonic, naphtoic, oxalic, palmitic, phenylacetic, propionic, pyridyl hydroxy pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, 2-hydroxyethane sulphonic,

toluene-p-sulphonic, and xinafoic acids. The term "pharmaceutically acceptable salts" also includes any pharmaceutically acceptable base salt such as amine salts, trialkyl amine salts and the like.

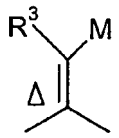
In addition to the pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification.

It will be appreciated that the compounds of the invention can contain one or more asymmetric carbon atoms which gives rise to isomers. In the compound of formula I the "*" designates an asymmetric carbon atom in this compound. Preferably, the compound of formula I has the following spatial orientation:



wherein, A, M, R^3 and R^4 are as defined above. It will be appreciated that the specific configuration of the carbon to which A is attached, namely "R" or "S", will depend upon the definition of R^3, M and Y and their respective priorities according to the Cahn-Ingold-Prelog sequence rules as described in J. March, Fourth Edition, Chapter 4, page 109. Where M is other than hydrogen an additional chiral center at the connecting carbon atom is generated. At this centre the compounds of formula I may be present as a racemate or in the "R" or "S" configuration. Racemic mixtures, enantiomers, diastereomers and individual isomers form part of the present invention, the compounds being employed as racemates or in enantiomerically pure form.

In accordance with this invention, for compounds of formula I where Z is



"Δ" denotes compounds wherein "A" and "M" have a trans configuration across the double bond.

The term "trans" as utilized in this application, designates that the two substituents attached at each end of the double bond are on opposite sides of the double bond.

As used throughout this application, the term "halogen" and the term "halo", unless otherwise stated, designate all four halogens, i.e. fluorine, chlorine, bromine and iodine. A preferred halogen is chlorine or fluorine. When R^1 and/or R^2 is halo, chlorine is especially preferred. When M is halo, fluorine is especially preferred.

As used herein, the term "lower alkyl" includes both straight chain and branched chain alkyl groups having from 1 to 7 carbon atoms, such as methyl, ethyl, propyl, isopropyl, preferably methyl and ethyl. With regard to R^3, isopropyl and n-propyl are preferred, isobutyl is also preferred.

As used herein, the term "Halo lower alkyl" designates a lower alkyl group wherein one or more of the hydrogens is replaced by a halogen as defined above, which replacement can be at any site on the lower alkyl, including the end, such as chloroethyl. With regard to R^3 fluoro lower alkyl is preferred.

As used herein, the term "Fluoro lower alkyl" designates a lower alkyl group wherein one or more of the hydrogens is replaced by fluorine, which replacement can be at any site on the lower alkyl, including the end, such as 1,1,1-trifluoroethane, 1,1,1-trifluoropropane and 1,1,1,3,3,3-hexafluoroisopropyl. A preferred fluoro lower alkyl group is 1,1,1,3,3,3-hexafluoroisopropyl.

The term "hydroxy lower alkyl" includes any hydroxy lower alkyl group where lower alkyl is defined as above. The hydroxy can be substituted at any place on the lower alkyl group such as hydroxy methyl, 1-hydroxy ethyl, 2-hydroxy propyl, 2-hydroxy isopropyl or 2-hydroxy-2-butyl. "Lower alkoxy lower alkyl" denotes any hydroxy lower alkyl group wherein the hydrogen of the hydroxy moiety is substituted by lower alkyl.

As used herein, "perfluoro-lower alkyl" means any lower alkyl group wherein all of the hydrogens of the lower alkyl group are substituted or replaced by fluoro. Among the preferred perfluoro-lower alkyl groups are trifluoromethyl, pentafluoroethyl, heptafluoropropyl, etc. An especially preferred perfluoro-lower alkyl group is trifluoromethyl.

As used herein, "lower alkyl thio" means a lower alkyl group as defined above where a thio group is bound to the rest of the molecule. Similarly "perfluoro-lower alkyl

thio" means a perfluoro-lower alkyl group as defined above where a thio group is bound to the rest of the molecule.

As used herein, "lower alkyl sulfonyl" means a lower alkyl group as defined above where a sulfonyl group is bound to the rest of the molecule, preferably lower alkyl sulfonyl is methyl sulfonyl. Similarly "perfluoro-lower alkyl sulfonyl" means a perfluoro-lower alkyl group as defined above where a sulfonyl group is bound to the rest of the molecule

As used herein, "hydroxyamino" designates an amino group where one of the hydrogens is replaced by a hydroxy.

As used herein, "cycloalkyl" means a saturated hydrocarbon ring having from 3 to 8 carbon atoms, preferably from 5 to 6 carbon atoms, such as cyclopentyl and cyclohexyl. An especially preferred cycloalkyl is cyclopentyl.

As used herein, "heterocycloalkyl" means a saturated hydrocarbon ring having from 3 to 8 carbon atoms, preferably from 5 to 7 carbon atoms, and having one to two heteroatoms which may be oxygen, sulfur or nitrogen. With regard to R^3 it is preferred to have a single heteroatom, preferably oxygen.

As used herein, "cycloalkenyl" means a cycloalkyl ring having from 3 to 8, and preferably from 5 to 7 carbon atoms, where one of the bonds between the ring carbons is unsaturated.

As used herein, the term "lower alkenyl" denotes an alkylene group having from 2 to 6 carbon atoms with a double bond located between any two adjacent carbons of the group, such as allyl and crotyl.

As used herein, the term "lower alkoxy" includes both straight chain and branched chain alkoxy groups having from 1 to 7 carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, preferably methoxy and ethoxy.

As used herein, the term "aryl" signifies aryl mononuclear aromatic hydrocarbon groups such as phenyl, tolyl, etc. which can be unsubstituted or substituted in one or more positions with halogen, nitro, lower alkyl, or lower alkoxy substituents and polynuclear aryl groups, such as naphthyl, anthryl, and phenanthryl, which can be unsubstituted or substituted with one or more of the aforementioned groups. Preferred aryl groups are the substituted and unsubstituted mononuclear aryl groups, such as phenyl.

As used herein, the term "arylalkyl" denotes an alkyl group, preferably lower alkyl, in which one of the hydrogen atoms is replaced by an aryl group. Examples of arylalkyl groups are benzyl, 2-phenylethyl, 3-phenylpropyl, 4-chlorobenzyl, 4-methoxybenzyl and the like.

As used herein, the term "lower alkanoic acid" denotes lower alkanoic acids containing from 2 to 7 carbon atoms such as propionic acid, acetic acid and the like. The term "lower alkanoyl" denotes monovalent alkanoyl groups having from 2 to 7 carbon atoms such as propionoyl, acetyl and the like. The term "aroic acids" denotes aryl alkanoic acids where aryl is as defined above and alkanoic contains from 1 to 6 carbon atoms. The term "aroyl" denotes aroic acids wherein aryl is as defined hereinbefore, with the hydrogen group of the COOH moiety removed. Among the preferred aroyl groups is benzoyl.

The heteroaromatic ring in R^4 can be an unsubstituted, mono- or di-substituted five- or six-membered heteroaromatic ring having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen or sulfur and connected by a ring carbon to the amine of the amide group shown. The heteroaromatic ring contains a first nitrogen heteroatom adjacent to the connecting ring carbon atom and if present, the other heteroatoms can be sulfur, oxygen or nitrogen. Heteroaromatic rings include, for example, pyrazinyl, pyridazinyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridinyl, pyrimidinyl, thiadiazolyl (preferably 1,3,4-, 1,2,3-, 1,2,4-), triazinyl (preferably 1,3,5-, 1,2,4-), thiazolyl, oxazolyl, and imidazolyl. The preferred heteroaromatic rings which constitute R^4 are connected *via* a ring carbon atom to the amide group to form the amides of formula I.

R^4 is preferably an unsubstituted, mono- or di-substituted five- or six-membered, heteroaromatic ring containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur, with one hetero atom being nitrogen and connected to the remainder of the molecule by a ring carbon atom. In this case, the preferred rings are those which contain a nitrogen heteroatom adjacent to the connecting ring carbon. When R^4 is an unsubstituted, mono- or di-substituted five- or six-membered heteroaromatic ring, the preferred rings are those which contain a nitrogen heteroatom adjacent to the connecting ring carbon and a second heteroatom adjacent to the connecting ring carbon or adjacent to said first heteroatom. Preferably R^4 is a five-membered

heteroaromatic ring. The preferred five-membered heteroaromatic rings contain 2 or 3 heteroatoms. Examples of such five-membered heteroaromatic rings are thiazolyl, imidazolyl, oxazolyl and thiadiazolyl, with thiazolyl being especially preferred.

When the heteroaromatic ring is a six-membered heteroaromatic, the ring is connected by a ring carbon atom to the amine group shown, with one nitrogen heteroatom being adjacent to the connecting ring carbon atom. The preferred six-membered heteroaromatic rings include, for example, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, and triazinyl with pyridinyl being especially preferred.

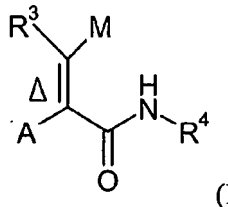
Above heteroaromatic rings R^4 may optionally be mono- or di-substituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting lower alkyl, halo, nitro, cyano, $-(CH_2)n-OR^{20}$, $-(CH_2)n-C(O)OR^{21}$, $-(CH_2)n-CONHR^{22}$, $-(CH_2)n-NHR^{23}$, with n, R^{20}, R^{21}, R^{22} and R^{23} being as defined above.

During the course of the synthetic sequence the various functional groups such as the free carboxylic acid or hydroxy groups will be protected *via* conventional hydrolyzable ester or ether protecting groups. As used herein the term "hydrolyzable ester or ether protecting groups" designates any ester or ether conventionally used for protecting carboxylic acids or alcohols which can be hydrolyzed to yield the respective hydroxyl or carboxyl group. Exemplary ester groups useful for those purposes are those in which the acyl moieties are derived from a lower alkanoic, aryl lower alkanoic, or lower alkane dicarboxcyclic acid. Among the activated acids which can be utilized to form such groups are acid anhydrides, acid halides, preferably acid chlorides or acid bromides derived from aryl or lower alkanoic acids. Example of anhydrides are anhydrides derived from monocarboxylic acid such as acetic anhydride, benzoic acid anhydride, and lower alkane dicarboxcylic acid anhydrides, e.g. succinic anhydride as well as chloro formats e.g. trichloro, ethylchloro formate being preferred. Suitable ether protecting groups for alcohols are, for example, the tetrahydropyranyl ethers such as 4-methoxy-5,6-dihydroxy-2H- pyranyl ethers. Others are aroylmethylethers such as benzyl, benzhydryl or trityl ethers or a-lower alkoxy lower alkyl ethers, for example, methoxymethyl or allylic ethers or alkyl silylethers such as trimethylsilylether.

As used herein, the term "amino protecting group" designates any conventional amino protecting group which can be cleaved to yield the free amino group. The preferred

protecting groups are the conventional amino protecting groups utilized in peptide synthesis. Especially preferred are those amino protecting groups which are cleavable under mildly acidic conditions at about pH 3.0. Particularly preferred amino protecting groupsare t-butoxycarbonyl (BOC), carbobenzyloxy (CBZ) and 9-flurorenylmethoxycarbonyl(FMOC).

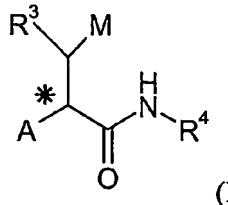
The compound of formula (I) of this invention constitutes two preferred species, i.e., the compound of formula



(I-A)

wherein A, B, R^3 and R^4 are as above;

and the compound of the formula



(I-B)

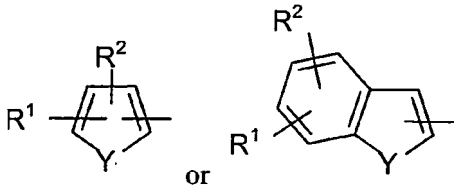
wherein A, M, R^3 and R^4 are as above.

In accordance with one preferable embodiment of the compound of formula I, R^3 is lower alkyl having from 2 to 6 carbon atoms, preferred lower alkyl residues being isopropyl and n-propyl. In one preferred embodiment R^3 is isopropyl, in another R^3 is isobutyl. In another preferable embodiment R^3 is $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms. In one preferred embodiment V is cyclopentyl, in another V is cyclohexyl. In another preferable embodiment R^3 is halo lower alkyl having from 2 to 6 carbon atoms, preferred halo lower alkyl residues being fluoro lower alkyl as defined above.

Preferred R^4 substituent in accordance with the present invention is where R^4 is R^{17} as defined above. Further preferred R^{17} substituents are unsubstituted, mono- or di-

substituted thiazolyl, imidazolyl, oxazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, and triazinyl. In one preferred embodiment R^{17} is thiazolyl, in another R^{17} is pyridinyl. In accordance with further preferable embodiments, the heteroaromatic ring R^{17} is either unsubstituted, mono- or di-substituted independently with lower alkyl, halogen or $-(CH_2)n-C(O)OR^{21}$, wherein n and R^{21} are as defined above. In another preferable embodiment M is hydrogen, halo or lower alkyl. Further preferred M subtituents are hydrogen, fluoro, methyl or ethyl. In one preferred embodiment M is hydrogen, in another M is methyl.

In accordance with another preferable embodiment of the compound of formula (I), A is



or

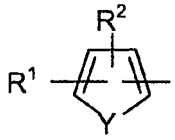
wherein Y and R^1 and R^2 are as defined above, the preferred Y substituent being sulfur. Preferred substituent R^1 is selected from the group consisting of hydrogen, halo, nitro, cyano, perfluoro lower alkyl, and lower alkyl sulfonyl. A further preferred R^1 substituent is selected from the group consisting of hydrogen, halo, nitro, cyano or perfluoro lower alkyl. In one preferred embodiment R^1 is halo, in another R^1 is hydrogen. Preferred substituent R^2 is selected from the group consisting of hydrogen, halo, nitro, cyano, perfluoro lower alkyl, lower alkyl sulfonyl, $R^{10}-[(CH_2)y-W]z$ and $R^{13}-(CH_2)t-U-$ where R^{10}, R^{13}, W, U, t, y and z are as defined above. Further preferred R^2 substituents are halo, lower alkyl sulfonyl, $R^{10}-[(CH_2)y-W]z$ and $R^{13}-(CH_2)t-U-$ where R^{10}, R^{13}, W, U, t, y and z are as defined above. In one preferred embodiment R^2 is lower alkyl sulfonyl, in another R^2 is $R^{10}-[(CH_2)y-W]z$ where R^{10}, W, U, y and z are as defined above, in another R^2 is $R^{13}-(CH_2)t-U-$ where R^{13}, U and t, are as defined above. In a further preferred embodiment R^2 is sulphonyl methyl, in another R^2 is $R^{10}-[(CH_2)y-W]z$ where W is SO_2 and R^{10}, U, y and z are as defined above.

In accordance with one embodiment of the compound of formula I-A, R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or

cyclohexyl (compound I-A1). Among the various embodiments of the compound I-A1 are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen. Another embodiment of the compounds of formula (I-A) are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-A2). Among the various embodiments of the compound I-A2 are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

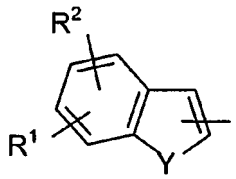
Among the embodiments of the compound of formula I-A, R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A3). Among the various embodiments of the compound I-A3 are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A, A is



where Y is sulfur (compound I-A4). Among the various embodiments of the compound I-A4 are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

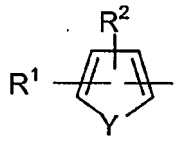
Among the embodiments of the compound of formula I-A, A is



where Y is sulfur (compound I-A5). Among the various embodiments of the compound I-A5 are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

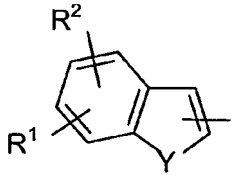
Among the embodiments of the compound of formula I-A1, R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A1(a)). Among the various embodiments of the compound I-A1(a) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A1, A is



where Y is sulfur (compound I-A1(b)). Among the various embodiments of the compound I-A1(b) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

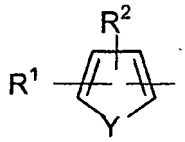
Among the embodiments of the compound of formula I-A1, A is



where Y is sulfur (compound I-A1(c)). Among the various embodiments of the compound I-A1(c) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

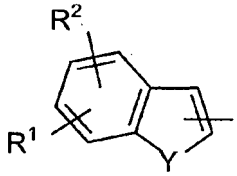
Among the embodiments of the compound of formula I-A2, R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A2(a)). Among the various embodiments of the compound I-A2(a) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A2, A is



where Y is sulfur (compound I-A2(b)). Among the various embodiments of the compound I-A2(b) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A2, A is

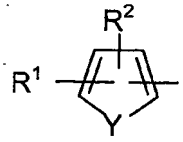


where Y is sulfur (compound I-A2(c)). Among the various embodiments of the compound I-A2(c) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3, R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-A3(a)). Among the various embodiments of the compound I-A3(a) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

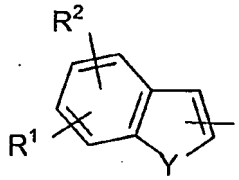
Among the embodiments of the compound of formula I-A3 are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-A3(b)). Among the various embodiments of the compound I-A3(b) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3, A is



where Y is sulfur (compound I-A3(c)). Among the various embodiments of the compound I-A3(c) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3, A is



where Y is sulfur (compound I-A3(d)). Among the various embodiments of the compound I-A3(d) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A4, R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-A4(a)). Among the various embodiments of the compound I-A4(a) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A4 are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-A4(b)). Among the various embodiments of the compound I-A4(b) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A4, R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A4(c)). Among the

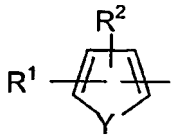
various embodiments of the compound I-A4(c) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A5, R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-A5(a)). Among the various embodiments of the compound I-A5(a) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A5 are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-A5(b)). Among the various embodiments of the compound I-A5(b) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

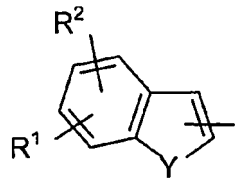
Among the embodiments of the compound of formula I-A5, R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A5(c)). Among the various embodiments of the compound I-A5(c) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A1(a), A is



where Y is sulfur (compound I-A1(a-1)). Among the various embodiments of the compound I-A1(a-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A1(a), A is

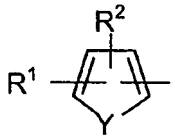


where Y is sulfur (compound I-A1(a-2)). Among the various embodiments of the compound I-A1(a-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A1(b), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A1(b-1)). Among the various embodiments of the compound I-A1(b-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

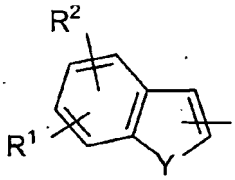
Among the embodiments of the compound of formula I-A1(c), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A1(c-1)). Among the various embodiments of the compound I-A1(c-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A2(a), A is



where Y is sulfur (compound I-A2(a-1)). Among the various embodiments of the compound I-A2(a-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A2(a), A is

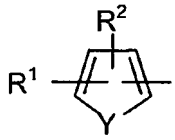


where Y is sulfur (compound I-A2(a-2)). Among the various embodiments of the compound I-A2(a-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A2(b), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A2(b-1)). Among the various embodiments of the compound I-A2(b-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

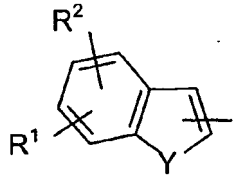
Among the embodiments of the compound of formula I-A2(c), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A2(c-1)). Among the various embodiments of the compound I-A2(c-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3(a), A is



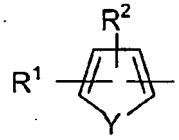
where Y is sulfur (compound I-A3(a-1)). Among the various embodiments of the compound I-A3(a-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3(a), A is



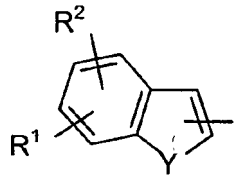
where Y is sulfur (compound I-A3(a-2)). Among the various embodiments of the compound I-A3(a-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3(b), A is



where Y is sulfur (compound I-A3(b-1)). Among the various embodiments of the compound I-A3(b-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3(b), A is



where Y is sulfur (compound I-A3(b-2)). Among the various embodiments of the compound I-A3(b-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3 (c), R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-A3(c-1)). Among the various embodiments of the compound I-A3(c-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3(c) are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-A3(c-2)). Among the various embodiments of the compound I-A3(c-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3 (d), R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-A3(d-1)). Among the various embodiments of the compound I-A3(d-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A3(d) are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-A3(d-2)). Among the various embodiments of the compound I-A3(d-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A4(a), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A4(a-1)). Among the various embodiments of the compound I-A4(a-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A4(b), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A4(b-1)). Among the various embodiments of the compound I-A4(b-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A4 (c), R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-A4(c-1)). Among the various embodiments of the compound I-A4(c-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A4(c) are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-A4(c-2)). Among the various embodiments of the compound I-A4(c-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A5(a), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A5(a-1)). Among the various embodiments of the compound I-A5(a-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A5(b), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-A5(b-1)). Among the various embodiments of the compound I-A5(b-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

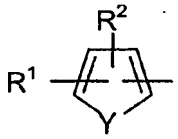
Among the embodiments of the compound of formula I-A5(c), R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-A5(c-1)). Among the various embodiments of the compound I-A5(c-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-A5(c) are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-A5(c-2)). Among the various embodiments of the compound I-A5(c-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

In accordance with one embodiment of the compound of formula I-B, R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-B1). Among the various embodiments of the compound I-B1 are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen. Another embodiment of the compounds of formula I-B are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-B2). Among the various embodiments of the compound I-B2 are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

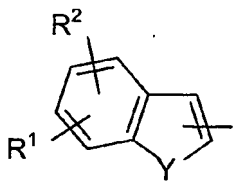
Among the embodiments of the compound of formula I-B, R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B3). Among the various embodiments of the compound I-B3 are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B, A is



where Y is sulfur (compound I-B4). Among the various embodiments of the compound I-B4 are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

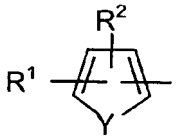
Among the embodiments of the compound of formula I-B, A is



where Y is sulfur (compound I-B5). Among the various embodiments of the compound I-B5 are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

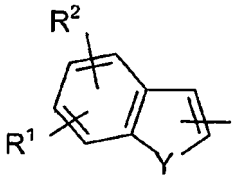
Among the embodiments of the compound of formula I-B1, R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B1(a)). Among the various embodiments of the compound I-B1(a) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B1, A is



where Y is sulfur (compound I-B1(b)). Among the various embodiments of the compound I-B1(b) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

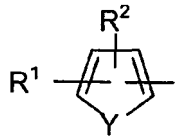
Among the embodiments of the compound of formula I-B1, A is



where Y is sulfur (compound I-B1(c)). Among the various embodiments of the compound I-B1(c) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

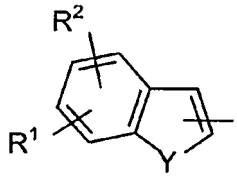
Among the embodiments of the compound of formula I-B2, R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B2(a)). Among the various embodiments of the compound I-B2(a) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B2, A is



where Y is sulfur (compound I-B2(b)). Among the various embodiments of the compound I-B2(b) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B2, A is



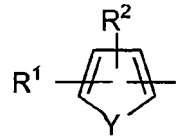
where Y is sulfur (compound I-B2(c)). Among the various embodiments of the compound I-B2(c) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3, R^3 can be $-(CH_2)s$-V where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-B3(a)). Among the various embodiments of the compound I-B3(a) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3 are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues

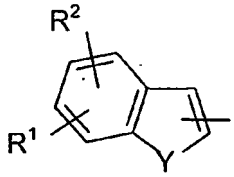
being isobutyl or isopropyl (compound I-B3(b)). Among the various embodiments of the compound I-B3(b) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3, A is



where Y is sulfur (compound I-B3(c)). Among the various embodiments of the compound I-B3(c) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3, A is



where Y is sulfur (compound I-B3(d)). Among the various embodiments of the compound I-B3(d) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B4, R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-B4(a)). Among the various embodiments of the compound I-B4(a) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B4 are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-B4(b)). Among the various embodiments of the compound I-B4(b) are included those compounds where M is hydrogen, halo or lower

alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

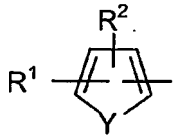
Among the embodiments of the compound of formula I-B4, R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B4(c)). Among the various embodiments of the compound I-B4(c) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B5, R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-B5(a)). Among the various embodiments of the compound I-B5(a) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B5 are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-B5(b)). Among the various embodiments of the compound I-B5(b) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

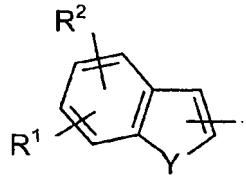
Among the embodiments of the compound of formula I-B5, R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B5(c)). Among the various embodiments of the compound I-B5(c) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B1(a), A is



where Y is sulfur (compound I-B1(a-1)). Among the various embodiments of the compound I-B1(a-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B1(a), A is

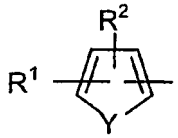


where Y is sulfur (compound I-B1(a-2)). Among the various embodiments of the compound I-B1(a-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B1(b), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B1(b-1)). Among the various embodiments of the compound I-B1(b-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

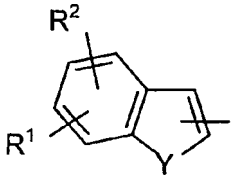
Among the embodiments of the compound of formula I-B1(c), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B1(c-1)). Among the various embodiments of the compound I-B1(c-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B2(a), A is



where Y is sulfur (compound I-B2(a-1)). Among the various embodiments of the compound I-B2(a-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B2(a), A is

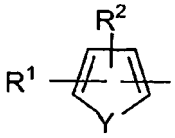


where Y is sulfur (compound I-B2(a-2)). Among the various embodiments of the compound I-B2(a-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B2(b), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B2(b-1)). Among the various embodiments of the compound I-B2(b-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

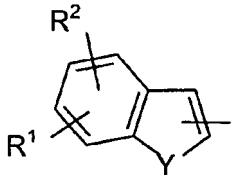
Among the embodiments of the compound of formula I-B2(c), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B2(c-1)). Among the various embodiments of the compound I-B2(c-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3(a), A is



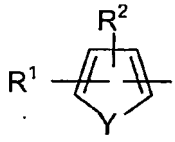
where Y is sulfur (compound I-B3(a-1)). Among the various embodiments of the compound I-B3(a-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3(a), A is



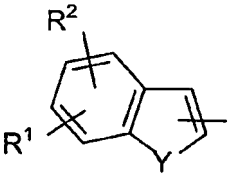
where Y is sulfur (compound I-B3(a-2)). Among the various embodiments of the compound I-B3(a-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3(b), A is



where Y is sulfur (compound I-B3(b-1)). Among the various embodiments of the compound I-B3(b-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3(b), A is



where Y is sulfur (compound I-B3(b-2)). Among the various embodiments of the compound I-B3(b-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3 (c), R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl

group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-B3(c-1)). Among the various embodiments of the compound I-B3(c-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3(c) are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-B3(c-2)). Among the various embodiments of the compound I-B3(c-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3 (d), R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-B3(d-1)). Among the various embodiments of the compound I-B3(d-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B3(d) are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-B3(d-2)). Among the various embodiments of the compound I-B3(d-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B4(a), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B4(a-1)). Among the various embodiments of the compound I-B4(a-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B4(b), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those

compounds where R^{17} is a thiazole or pyridine ring (compound I-B4(b-1)). Among the various embodiments of the compound I-B4(b-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B4 (c), R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-B4(c-1)). Among the various embodiments of the compound I-B4(c-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B4(c) are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-B4(c-2)). Among the various embodiments of the compound I-B4(c-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B5(a), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B5(a-1)). Among the various embodiments of the compound I-B5(a-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B5(b), R^4 is R^{17}, which can be an unsubstituted, mono- or di-substituted thiazole, imidazole, oxazole, thiadiazole, pyridine, pyrimidine, pyrazine, pyridazine, or triazine ring, and particularly those compounds where R^{17} is a thiazole or pyridine ring (compound I-B5(b-1)). Among the various embodiments of the compound I-B5(b-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

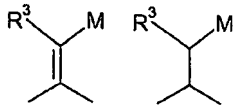
Among the embodiments of the compound of formula I-B5(c), R^3 can be $-(CH_2)s-V$ where "s" and "V" are as defined above, the preferred V substituent being a cycloalkyl

group which contains from 3 to 8 carbon atoms, preferably cyclopentyl or cyclohexyl (compound I-B5(c-1)). Among the various embodiments of the compound I-B5(c-1) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

Among the embodiments of the compound of formula I-B5(c) are those compounds where R^3 is lower alkyl having from 2 to 6 carbon atoms, preferably lower alkyl residues being isobutyl or isopropyl (compound I-B5(c-2)). Among the various embodiments of the compound I-B5(c-2) are included those compounds where M is hydrogen, halo or lower alkyl, particularly where M is hydrogen, fluoro or methyl, more particularly where M is hydrogen.

The compounds of the present invention may be prepared as is shown in the following reaction schemes.

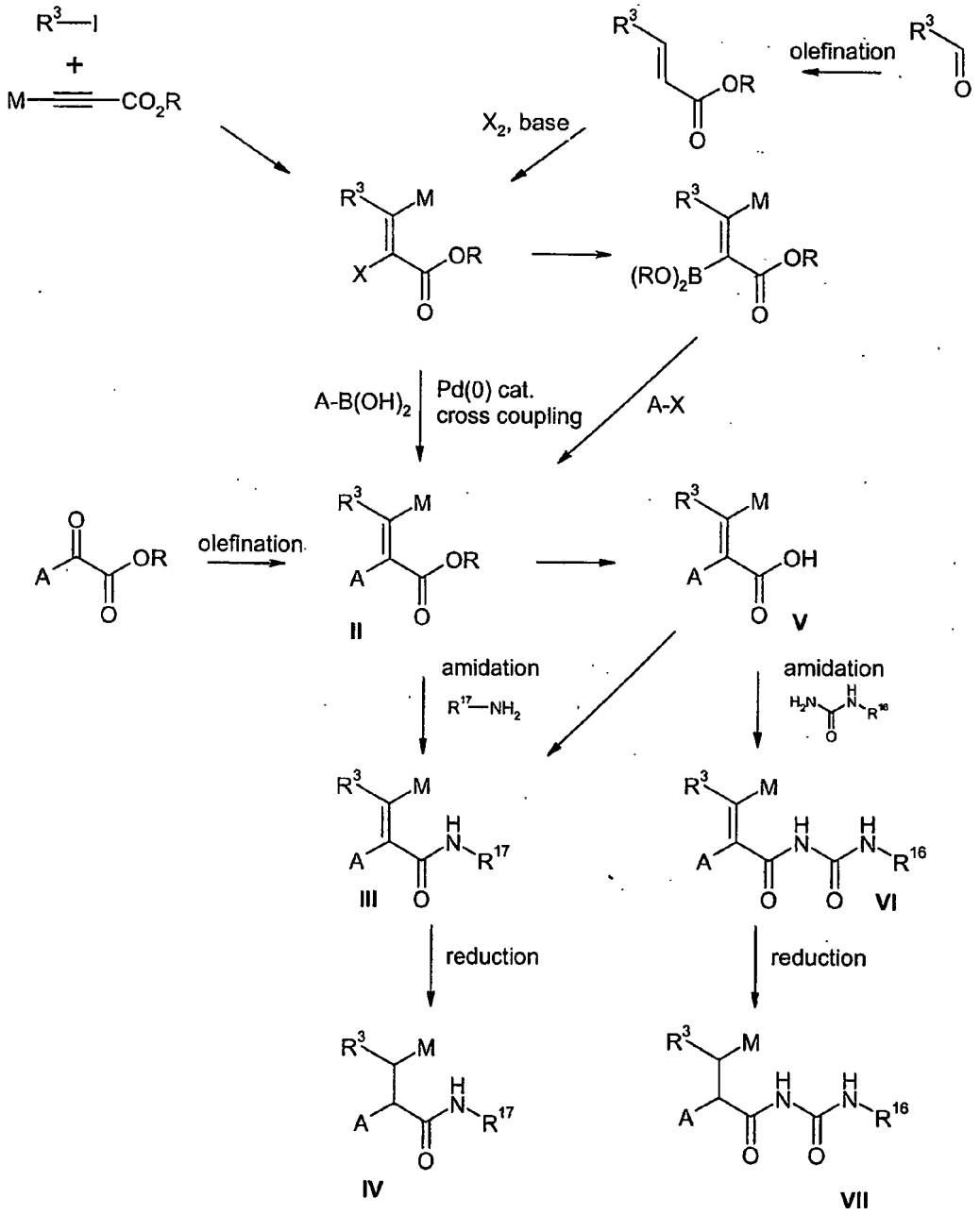
In the case when Z equals



the preparation of the compounds is outlined in Scheme I. The corresponding alkyl iodides are reacted with a propargyl ester to give the substituted 2-iodo alkenoates (see Y. Ichinose et al., *Tet. Lett.* **1989**, 24, 3155). Alternatively, compounds where M equals hydrogen, can be prepared by reacting aldehydes R^3-CHO with an appropriate Wittig reagent, preferedly triethyl phosphono acetate, to give the acrylic esters, which then are transformed into the 2-halo-alk-2-enoates by a halogenation / dehydro-halgenation procedure known in the art. Subsequent Pd(0)-catalyzed cross coupling with heteroaromatic boronic acids and boronic esters, respectively, yields the hetaryl-substituted alk-2-enoates of formula II. The latter intermediates can also be prepared from in situ formed olefinic boronic esters with the corresponding hetaryl bromides and iodides. For the preparation of compounds of formula II where M equals halo, the (hetero)aryl substituted α-keto ester may be reacted with the appropriate halo-substituted organophosphonate using conditions known in the art. In order to prepare amides of formula III, these can be directly reacted with the deprotonated amines R^{17}-NH_2, using appropriate Grignard reagents, preferably isopropyl magnesium chloride. Alternatively, alkenoates of formula II can be hydrolyzed to the corresponding acids of formula V by

known procedures of alkaline or acidic saponification. Subsequent activation of the acids by known means in the area of peptide coupling, followed by reaction with amines R^{17}-NH_2 also yield the amides of formula III. For the synthesis of amides of the formula VI, the acids are reacted with substituted ureas H_2N-CO-NH-R^{16}. Reduction of compounds of formula III and VI can be carried out using hydride reagents, preferably sodium borohydride, to afford the saturated alkanoate amides of formula IV and VII.

Scheme I


R3—I
+
M—≡—CO2R
X2, base
olefination
OR
O
X
(RO)2B
A-B(OH)2
Pd(0) cat.
cross coupling
A-X
A
II
V
amidation
R17—NH2
III
VI
reduction
IV
VII

Experimentals:

General Procedures:

All water or air-sensitive reactions were conducted in dry solvents under an inert atmosphere. Mass spectra (MS) were obtained on a Agilent 1100 MSD spectrometer operating in electrospray mode or on a Agilent 5973N GC-MSD.

List of abbreviations:

THF	tetrahydrofuran
DMSO	dimethylsulfoxide
TBTU	O-benzotriazol-1-yl-N,N,N',N' tetramethyluroniumtetrafluoroborate
HATU	O-(7-Aza-1-benzotriazolyl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate
DMF	N,N-dimethylformamide
NMP	1-methyl-2-pyrrolidinone
brine	saturated aqueous sodium chloride solution
r.t.	room temperature / ambient temperature
TBME	2-methoxy-2-methyl-propane
DMA	*N,N*-dimethyl-acetamide
HPLC	high pressure liquid chromatography
TFA	trifluoroacetic acid
NH_3	ammonia
HOAt	1-hydroxy-7-azabenzotriazole
MTB ether	2-methoxy-2-methyl-propane

General Procedure I for the preparation of substituted 2-iodo-alk-2-enoates:

The alkyl iodides mentioned below were reacted with ethyl propiolate in the presence of triethylborane as described (Y. Ichinose et al., Tet. Lett. 1989, 30(24), 3155-3158)

(Z)-Ethyl 3-cyclohexyl-2-iodo-propenoate, MS(EI), M^+= 308,

reagent used: cyclohexyl iodide

(Z)-Ethyl 3-cyclopentyl-2-iodo-propenoate, MS(EI), M^+= 294,

reagent used: cyclopentyl iodide

(Z)-Ethyl 2-iodo-4-methyl-pent-2-enoate, MS(EI), M^+= 268,
reagent used: 2-iodo-propane

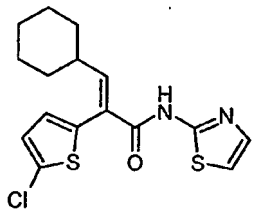
General procedure II for the preparation of compounds of formula I:

Add the heteroaromatic boronic acid (1.2 equiv. to vinyl halide) to a stirred mixture of vinyl halide, palladium catalyst (5 mol%) and potassium carbonate (2.5 equiv) in toluene (3ml / 1.0 mmol vinyl halide) and heat the mixture at 70 °C for 14h. Subsequently filter the mixture, add water and extract with MTB ether. Combine the organic layers, dry over sodium sulfate and concentrate under reduced pressure. Dissolve the crude product in ethanol (2 ml/mmol), add 2N sodium hydroxide solution (2ml/mmol) and heat at 70 °C for 14h. Acidify with 1N hydrochloric acid, extract with MTB ether, dry combined organic layers over sodium sulfate and concentrate under reduced pressure. Dissolve the crude product in THF (3ml/mmol), add TBTU (1.5 equiv), triethylamine (2 equiv.) and the respective amine (1.5 equiv.) and stir for 14h at ambient temperature. Aqueous work-up using saturated sodium hydrogencarbonate solution / saturated citric acid and extraction with MTB ether gives the crude product. Purification by flash chromatography (silica) eluting with a mixture of hexanes / ethyl acetate yields the title compounds.

The following Examples illustrate compounds of the present invention and methods for their synthesis.

Example 1:

(E)-3-Cyclohexyl-2-(5-chloro-thiophen-2-yl)-N-thiazol-2'-yl-propenylamide



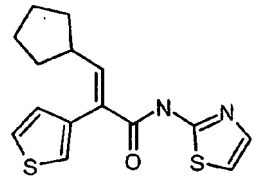
a) (E)-3-Cyclohexyl-2-(5-chloro-thiophen-2-yl)-propenoic acid:
reaction of 5-Chloro-thiophen-2-yl-boronic acid (0.63g, 3.9 mmol) with (Z)-Ethyl 3-cyclohexyl-2-iodo-propenoate (1.0g, 3.25 mmol) using $Pd(dba)_2$ as catalyst as outlined in

General Procedure II.

b) (E)-3-Cyclohexyl-2-(5-chloro-thiophen-2-yl)-N-thiazol-2'-yl-propenylamide: reaction of 2-aminothiazole (0.35, 3.47mmol) with compound 1a) according to General Procedure II, 0.13g of a yellowish solid, MS(M^++H)=353.

Example 2:

(E)-3-Cyclopentyl-2-(thiophen-3-yl)-N-thiazol-2'-yl-propenylamide

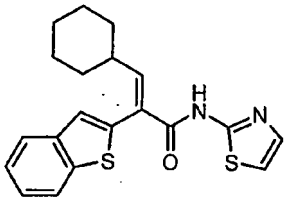


a) (E)-3-Cyclopentyl-2-(thiophen-3-yl)-propenoic acid:
reaction of thiophen-3-yl boronic acid (0.16g, 1.22 mmol) with (Z)-Ethyl 3-cyclopentyl-2-iodo-propenoate (0.30g, 1.02 mmol) using $Pd(dba)_2$ as catalyst as outlined in General Procedure II.

b) (E)-3-Cyclohexyl-2-(5-chloro-thiophen-2-yl)-N-thiazol-2'-yl-propenylamide: reaction of 2-aminothiazole (0.13g, 1.22 mmol) with compound 2a) according to General Procedure II, 0.53g of a yellowish solid, MS(M^++H)=305.

Example 3:

(E)-3-Cyclohexyl-2-(benzothiophen-2-yl)-N-thiazol-2'-yl-propenylamide



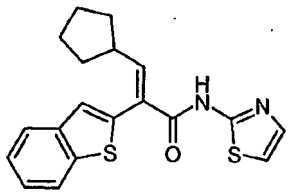
a) (E)-3-Cyclohexyl-2-(benzothiophen-2-yl)-propenoic acid :
reaction of thiophen-3-yl boronic acid (0.69 g, 3.90 mmol) with (Z)-Ethyl 3-cyclohexyl-2-iodo-propenoate (1.0 g, 3.25 mmol) using $Pd(dba)_2$ as catalyst as outlined in General Procedure II.

b) (E)-3-Cyclohexyl-2-(benzothiophen-2-yl)-N-thiazol-2'-yl-propenylamide: reaction of 2-aminothiazole (0.30g, 3.0 mmol) with compound 3a) according to General

Procedure II, 0.40g of a solid, MS(M^++H)=369.

Example 4:

(E)-3-Cyclopentyl-2-(benzothiophen-2-yl)-N-thiazol-2'-yl-propenylamide



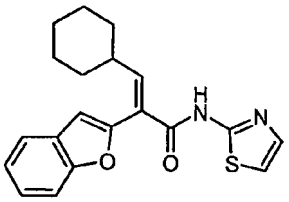
a) (E)-3-Cyclopentyl-2-(benzothiophen-2-yl)-propenoic acid

reaction of benzothiophen-2-yl boronic acid (0.22g, 1.22 mmol) with (Z)-Ethyl 3-cyclopentyl-2-iodo-propenoate (0.30g, 1.02 mmol) using $Pd(dba)_2$ as catalyst as outlined in General Procedure II.

b) (E)-3-Cyclopentyl-2-(benzothiophen-2-yl)-N-thiazol-2'-yl-propenylamide: reaction of 2-aminothiazole (0.11g, 1.06 mmol) with compound 4a) according to General Procedure II, 0.05g of a yellowish solid, MS(M^++H)=355.

Example 5:

(E)-3-Cyclohexyl-2-(benzofuran-2-yl)-N-thiazol-2'-yl-propenylamide



a) (E)-3-Cyclohexyl-2-(benzofuran-2-yl)-propenoic acid:

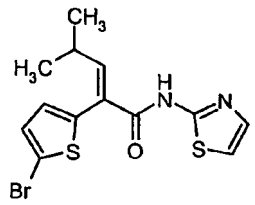
reaction of benzofuran-2-yl-boronic acid (0.63g, 3.89 mmol) with (Z)-Ethyl 3-cyclohexyl-2-iodo-propenoate (1.0g, 3.25 mmol) using $Pd(dba)_2$ as catalyst as outlined in General Procedure II.

b) (E)-3-Cyclohexyl-2-(benzofuran-2-yl)-N-thiazol-2'-yl-propenylamide:

reaction of 2-aminothiazole (0.28, 2.80 mmol) with compound 5a) according to General Procedure II, 0.18 g of a yellowish solid, MS(M^++H)=353.

Example 6:

(E)-4-Methyl-2-(5-bromo-thiophen-2-yl)-N-thiazol-2'-yl-pent-2-enylamide

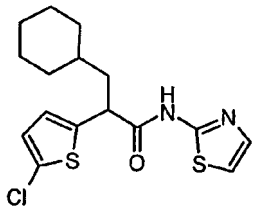


a) (E)-4-Methyl-2-(5-bromo-thiophen-2-yl)-propenoic acid:
5-Bromo-thiophen-2-yl-zinc bromide (7.46 ml of a 0.5M solution in THF, 3.73 mmol) was added under argon atmosphere to a mixture containing (Z)-Ethyl 2-iodo-4-methyl-pent-2-enoate (0.5 g, 1.86 mmol), Pd(dppf)Cl_2 (136 mg, 10 mol%) and copper(I) iodide (30mg, 10 mol%) in 5ml of anhydr. THF. The mixture was stirred at reflux temperature for 14h. After cooling, the reaction was quenched with 1N hydrochloric acid, followed by extraction with methylene dichloride. Hydrolysis of the ester was achieved as described according to the General procedure II.

b) (E)-3-Cyclohexyl-2-(5-chloro-thiophen-2-yl)-N-thiazol-2'-yl-propenylamide: reaction of 2-aminothiazole (0.16, 1.60 mmol) with compound 8a) according to General Procedure II, 0.02 g of a yellowish solid, MS(M^++H)=358.

Example 7:

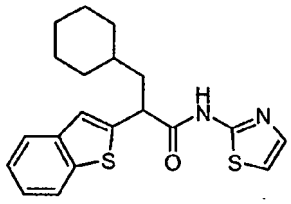
(E)-3-Cyclohexyl-2-(5-chloro-thiophen-2-yl)-N-thiazol-2'-yl-propionamide



Compound 1b (0.11 g, 0.31 mmol) was dissolved in 2 ml of dry THF/EtOH (1:1), sodium borohydride (0.05 g, 1,32 mmol) was added at ambient temperature, and the reaction mixture was stirred for 14h. Aqueous work-up and extraction with ethyl acetate gave a yellowish gum after evaporation, which crystallized from acetonitrile to yield 22 mg of a colorless solid, MS(M^++H)=355.

Example 8:

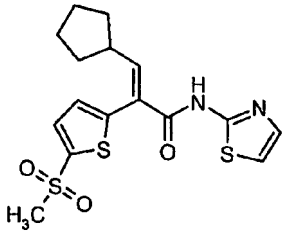
(E)-3-Cyclohexyl-2-(benzothiophen-2-yl)-N-thiazol-2'-yl-propionamide



Compound 3b) (0.23 g, 0.62 mmol) was dissolved in 4 ml of dry THF/EtOH (1:1) and sodium borohydride (0.095 g, 2.51 mmol) was added at ambient temperature and stirred for 14h. Aqueous work-up and extraction with ethyl acetate gave a yellowish gum after evaporation, which crystallized from acetonitrile to yield 85 mg of a colorless solid, MS(M^++H)=371.

Example 9:

(E)-3-Cyclopentyl-2-(5-methylsulfonyl-thiophen-2-yl)-N-thiazol-2'-yl-propenylamide



a) Ethyl (E)-3-Cyclopentyl-2-(5-methylsulfonyl-thiophen-2-yl)-propenoate:
Ethyl (Z)-3-cyclopentyl-2-iodo-propenoate (0.1g, 0.34 mmol) was dissolved in 2 ml of DMSO. Bis(pinacolato)diborane (0.093 g, 0.37 mmol), potassium acetate (0.1 g, 1.02 mmol) and Pd(dppf)Cl_2 (0.02g) were added at ambient temperature and then stirred for 2h at 80°C under argon atmosphere. After cooling, the mixture was added dropwise via a syringe to a solution of 2-iodo-5-methylsulfonyl-thiophene (0.036g, 0.12 mmol) in 2M sodium carbonate (0.29 ml) / DMSO (1 ml) at 50°C and stirred for an additional 1.5h. Aqueous work-up, extraction with ethyl acetate, drying over sodium sulfate and evaporation gave the crude product.

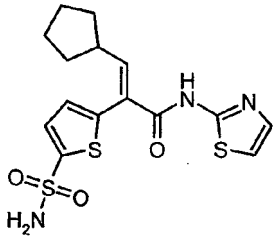
b) (E)-3-Cyclopentyl-2-(5-methylsulfonyl-thiophen-2-yl)-N-thiazol-2'-yl-propenylamide:

To a solution of 2-aminothiazole (0.048g, 0.48 mmol) in THF (1 ml) was added isopropylmagnesium chloride (0.24 ml of a 2M solution in THF, 0.48 mmol) at -35°. The mixture was warmed and stirred under argon at ambient temperature for 1h. After cooling to -35°C, crude compound 9a) (0.09g, 0.12 mmol) was added dropwise and stirred at 50°C overnight. Work-up with sat. ammonium chloride solution, extraction with ethyl acetate, drying over sodium sulfate and evaporation gave the crude product.

RP-chromatography using water/acetonitrile as eluent system gave 15 mg of a yellowish solid, MS(M^++H)=383.

Example 10:

(E)-3-Cyclopentyl-2-(5-sulfamoyl-thiophen-2-yl)-N-thiazol-2'-yl-propenylamide



a) 5-Bromo-thiophen-2-sulfonic acid dimethylaminomethylene amide: to a solution of 5-bromo-2-thiophen sulfonamide (0.3 g, 1.24 mmol) in abs. DMF (3 ml) was added N,N-dimethylformamide dimethylacetal (0.17 ml, 1.24 mmol), and the reaction mixture was stirred at ambient temperature overnight. Aqueous work-up, extraction with ethyl acetate, drying over sodium sulfate and evaporation gave the crude product as a colorless crystalline solid.

b) Ethyl (E)-3-Cyclopentyl-2-[(5-dimethylaminomethylene sulfamoyl)-thiophen-2-yl]-propenoate: processed as described for compound 9a), using (Z)-Ethyl 3-cyclopentyl-2-iodo-propenoate (0.44g, 1.49 mmol), compound 12a) (0.35g), bis(pinacolato)diborane (0.42 g, 1.64 mmol), potassium acetate (0.44 g, 4.47 mmol) and Pd(dppf)Cl_2 (0.066g).

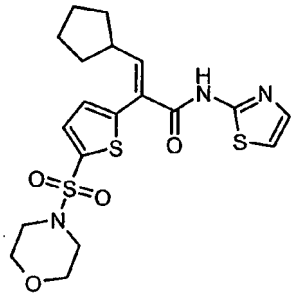
c) (E)-3-Cyclopentyl-2-[(5-dimethylaminomethylene sulfamoyl)-thiophen-2-yl)-N-thiazol-2'-yl-propenoate: processed as described for compound 9b), using compound 10b) (0.61g, 1.59 mmol), 2-aminothiazole (0.47g, 4.72 mmol), isopropylmagnesium chloride (2.36 ml of a 2M solution in THF, 4.72 mmol).

d) (E)-3-Cyclopentyl-2-(5-sulfamoyl-thiophen-2-yl)-N-thiazol-2'-yl-propenylamide: Compound 10c) (0.04g, 0.09mmol) was dissolved in a solution of ethanol / 5N HClaq (5

ml, 1:1 v:v) and heated at 80°C for 2h. Subsequent work-up with sat. sodium hydrogencarbonate solution and extraction with ethyl acetate yielded the crude product. Flash chromatography using methylene chloride/ethanol 98/2 as eluent system gave the product as a colorless solid, MS(M^++H)=384.

Example 11:

(E)-3-Cyclopentyl-2-(5-N-morpholinosulfonyl-thiophen-2-yl)-N-thiazol-2'-yl-propenylamide

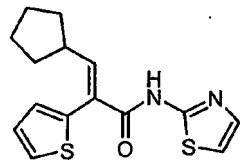


a) Ethyl (E)-3-Cyclopentyl-2-(5-N-morpholinosulfonyl-thiophen-2-yl)-propenoate: processed as described for compound 9a), using (Z)-Ethyl 3-cyclopentyl-2-iodo-propenoate (0.1g, 0.36 mmol), 2-bromo-5-N-morpholinosulfonyl-thiophen (0.078g, 0.25 mmol), bis(pinacolato)diborane (0.42 g, 1.64 mmol), potassium acetate (0.11 g, 1.1 mmol) and Pd(dppf)Cl_2 (0.04g).

b) (E)-3-Cyclopentyl-2-(5-N-morpholinosulfonyl-thiophen-2-yl)-N-thiazol-2'-yl-propenylamide: processed as described for compound 9a), using compound 11a) (0.2g, 0.25 mmol), 2-aminothiazole (0.14g, 1.44 mmol), isopropylmagnesium chloride (0.72 ml of a 2M solution in THF, 1.44 mmol). Flash chromatography using hexanes/ethyl ester 9/1 as eluent system gave the product, MS(M^++H)=454.

Example 12:

(Z)-3-Cyclopentyl-N-thiazol-2-yl-2-thiophen-3-yl-acrylamide:



a) (Z)-3-Cyclopentyl-2-thiophen-3-yl-acrylic acid: 5-Bromo-thiophen-2-yl-zinc bromide (20.4 ml of a 0.5M solution in THF, 10.2 mmol) was added under argon atmosphere to a mixture containing (Z)-ethyl 2-iodo-4-methyl-pent-2-enoate (1.5 g, 5.1 mmol), $Pd(dppf)Cl_2$ (373 mg, 10 mol%) and copper(I) iodide (60 mg, 16 mol%) in 5 ml of anhydr. THF. The mixture was stirred at 75°C for 14h. After cooling, the reaction mixture was quenched with 1N hydrochloric acid, and extracted with MTB ether to afford 1.5 g of a red residue after removal of volatiles. This material was taken up in a mixture of EtOH (20 mL) and 2 N aqueous sodium hydroxide solution (20 mL). The resulting reaction mixture was stirred at 75°C for 14h, cooled, and poured onto 1 N aqueous hydrochloric acid. The resulting mixture was extracted with MTB ether. The extracts were dried over sodium sulfate and concentrated to afford 1.24 g of impure (Z)-3-cyclopentyl-2-thiophen-3-yl-acrylic acid.

b) (Z)-3-Cyclopentyl-N-thiazol-2-yl-2-thiophen-3-yl-acrylamide: reaction of 2-aminothiazole (0.16 g, 1.62 mmol) with compound 12a) (0.3 g, 1.35 mmol) according to General Procedure II, 94 mg of a solid, $MS(M^+H)=305$

The compounds of the present invention may be used as medicaments in human or veterinary medicine. The compounds may be administered by various routes, for example, by oral or rectal routes, topically or parenterally, for example by injection, and are usually employed in the form of a pharmaceutical composition.

Such compositions may be prepared by methods well known in the pharmaceutical art and normally comprise at least one active compound in association with a pharmaceutically acceptable diluent or carrier. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container. Where the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of tablets, lozenges, sachets, cachets, elixirs, suspensions, solutions, syrups, aerosol (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, injection solutions and suspensions and sterile packaged powders.

Some examples of suitable carriers are lactose, dextrose, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as starch and petroleum jelly, sucrose sorbitol, mannitol, starches, gum acacia,calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl- hydrobenzoate, talc, magnesium stearate and mineral oil. The compounds of formula (I) can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds, e.g. one or more vitamins. Compositions of the invention may be formulated so as to provide, quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 500 mg, more usually about 25 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary doses for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

Example A

Tablets containing the following ingredients can be produced in a conventional manner:

Ingredients (mg per capsule)	
Compound of formula I	10.0 - 100.0
Lactose	125.0
Corn starch	75.0
Talc	4.0
Magnesium stearate	1.0

Example B

Capsules containing the following ingredients can be produced in a conventional manner:

Ingredients (mg per capsule)	
Compound of formula I	25.0
Lactose	150.0
Corn starch	20.0
Talc	5.0

The pharmacological profile of the present compounds may be demonstrated as follows:

An enzymatic coupled glucokinase (GK) assay using purified recombinant human islet GK was used to evaluate effects of the activators. In this assay, GK catalyzes glucose phosphorylation in the presence of ATP. The product of this reaction, glucose-6-phosphate, is then oxidized by an excess of glucose-6-dehydrogenase to produce gluconate-6-phosphate with concomitant reduction of NAD^+ to NADH (Davidson and Arion, 1987). The following outlines the two reactions involved:

Glucose + ATP → Glucose-6-P + ADP (Glucokinase)

Glucose-6-P + NAD → Gluconate-6-P + NADH (glucose-6-P dehydrogenase)

The NADH production detected by absorbance at 340nm is used to monitor the enzymatic activity.

The human islet GK isoform was expressed in *E.coli* as $(His)_6$ -tagged fusion protein and purified with metal chelate affinity chromatography (Tiedge et al., 1997). After purification the enzyme was stored in aliquots at concentration 0.8 mg/ml in 25 mM NaH_2PO_4, 150 mM NaCl, 100 mM imidazole, 1 mM DTT, 50 % glycerol at -80°C.

The assay was performed in flat bottom 96-well plates in a final incubation volume of 100µl. The incubation mixture consisted of 25 mM HEPES (pH7.4), 50 mM KCl, 2.5 mM $MgCl_2$, 2 mM dithiothreitol, 4 U/ml glucose-6-phosphate dehydrogenase from *Leuconostoc mesenteroides*, 5 mM ATP, 1 mM NAD and 10 mM glucose. All reagents were from Sigma-Aldrich Co. (St. Louis, MO). Test compounds were dissolved in DMSO and then added to the reaction mixture giving the final DMSO concentration of 10%.

The reaction was initiated by addition of 20 µl GK and run for 20 min at 37°C. The amount of formed NADH was measured as an increase in absorbance at 340 nm using a microplate reader.

The concentration of activator that produced 50% of the maximum increase in the activity of GK (EC_{50}) was calculated The preferred compounds of formula I described within the examples have an EC_{50} less than or equal to 30 µM.

EXAMPLE	EC50 (µM)
1	1.840
3	1.532
5	1.824
9	2.002
10	1.263
11	0.909
12	5.598

EC50 values shown in the above table are at 10mM glucose.

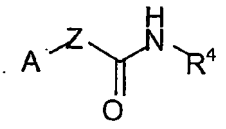
References:

Davidson A.L. and Arion W.J. Factors underlying significant underestimations of glucokinase activity in crude liver extracts: physiological implications of higher cellular activity. Arch. Biochem. Biophys. 253, 156-167, 1987.

Tidge M, Krug U. and Lenzen S. Modulation of human glucokinase intristic activity by SH reagents mirrors post-translational regulation of enzyme activity. Biochem. Biophys. Acta 1337, 175-190, 1997.

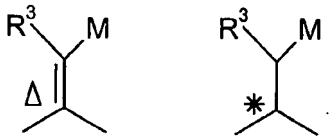
Claims

1. A compound of formula



(I)

wherein Z is

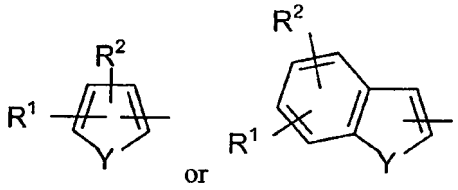


R^3 is lower alkyl or halo lower alkyl having from 2 to 6 carbon atoms or arylalkyl or –(CH_2)s-V where V is a 3 to 8-membered ring which is cycloalkyl, cycloalkenyl, or heterocycloalkyl having one heteroatom selected from oxygen and sulfur;

s is independently 0, 1 or 2;

M is hydrogen or halo or lower alkyl or perfluoro-lower alkyl;

A is



where Y is oxygen or sulfur, and

R^1 and R^2 are independently hydrogen, halo, amino, hydroxyamino, nitro, cyano, sulfonamido, lower alkyl, $-OR^5$, $-COOR^5$, perfluoro- lower alkyl, lower alkyl thio, perfluoro-lower alkyl thio, lower alkyl sulfonyl, perfluoro-lower alkyl sulfonyl, lower alkyl sulfinyl,

R^5 is hydrogen, lower alkyl or perfluoro-lower alkyl; or furthermore

R^2 can be $-(CH_2)n-NR^6R^7$, with n=1,2,3 or 4, and

R^6 and R^7 are independently hydrogen or lower alkyl; or together with the nitrogen atom to which they are attached form a five or six-membered heteroaromatic ring containing from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen; or a saturated 5- or 6-membered cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen; or

R^2 can be alkinyl,

substituted with hydrogen, lower alkyl, hydroxy lower alkyl, lower alkoxy lower alkyl, an unsubstituted or hydroxy substituted cycloalkyl ring containing 5 or 6 carbon atoms, a five- or six-membered saturated heterocyclic ring which contains from 1 to 3 hetero atoms selected from the group consisting of sulfur, oxygen or nitrogen, or an unsubstituted five- or six-membered heteroaromatic ring, connected by a ring carbon atom, which contains from 1 to 3 heteroatoms in the ring selected from the group consisting of sulfur, nitrogen and oxygen, or $-(CH_2)n-NR^8R^9$, with n=1,2, and

R^8 and R^9 are independently hydrogen or lower alkyl; or together with the nitrogen atom to which they are attached form a five or six-membered heteroaromatic ring containing from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen; or a saturated 5- or 6-membered cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen; or

R^2 can be $R^{10}-[(CH_2)y-W]z-$, with

W is oxygen, sulfur, -SO-, $-SO_2-$, and

R^{10} is a heteroaromatic ring, connected by a ring carbon atom, which contains from 5 to 6 ring members with from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur or nitrogen, or

aryl containing 6 or 10 ring carbon atoms, or

aryl containing 6 ring carbon atoms fused with a heteroaromatic ring containing 5 or 6 ring members with 1 or 2 heteroatoms in the ring being selected from the group consisting of nitrogen, oxygen or sulfur, or

a saturated 5- or 6-membered cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, or

a cycloalkyl ring having 5 or 6 carbon atoms, or

$-NR^{11}R^{12}$, with R^{11} and R^{12} being independently hydrogen or lower alkyl;

y is independently 0,1,2,3 or 4; z is independently 0,1; or

R^2 can be R^{13}-(CH_2)t-U-, with

U is -NHCO-, -CONH, -$NHSO_2$-, -SO_2NH- and

R^{13} in the same meaning of R^{10} and

perfluoro-lower alkyl, lower alkyl, lower alkoxycarbonyl or

-$NR^{14}R^{15}$, R^{14} and R^{15} are independently hydrogen or lower alkyl; or together with the nitrogen atom to which they are attached form a five or six-membered heteroaromatic ring containing from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen; or a saturated 5- or 6- membered heterocycloalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen;

t is an integer being 0, 1, 2, 3 or 4;

R^4 is -C(O)NHR^{16}, or is R^{17};

R^{16} is hydrogen, lower alkyl, lower alkenyl, hydroxy lower alkyl,

-(CH_2)n-$COOR^{18}$, -CO-(CH_2)n-$COOR^{19}$;

R^{17} is an unsubstituted, mono- or di-substituted five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amide group shown, which five- or six-membered heteroaromatic ring contains from 1 to 4 heteroatoms selected from sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent to the connecting ring carbon atom; said mono- or di-substituted heteroaromatic ring being mono- or di-substituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, halo, nitro, cyano, -(CH_2)n-OR^{20}, -(CH_2)n-$COOR^{21}$,

-(CH_2)n-$CONHR^{22}$, -(CH_2)n-NHR^{23},

n is 0, 1, 2. 3 or 4;

R^{18}, R^{19}, R^{20}, R^{21}, R^{22} and R^{23} are independently hydrogen or lower alkyl,

and its pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein

R^4 is an unsubstituted, mono- or di-substituted five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amide group shown, which five- or six-membered heteroaromatic ring contains from 1 to 4 heteroatoms selected from sulfur, oxygen or nitrogen, with one heteroatom being nitrogen which is adjacent to the connecting ring carbon atom; said mono- or di-substituted heteroaromatic ring being mono- or di-

substituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, halo, nitro, cyano, -(CH_2)n-OR^{20}, -(CH_2)n-$COOR^{21}$, -(CH_2)n-$CONHR^{22}$, -(CH_2)n-NHR^{23},

n is 0, 1, 2. 3 or 4;

R^{20}, R^{21}, R^{22} and R^{23} are independently hydrogen or lower alkyl,

and its pharmaceutically acceptable salts thereof.

3. A compound according to any of claims 1 to 2, wherein R^4 is an unsubstituted, mono- or di-substituted five- or six-membered heteroaromatic ring selected from the group consisting of thiazolyl, imidazolyl, oxazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, or triazinyl.

4. A compound according to any of claims 1 to 3 wherein R^4 is thiazolyl or pyridinyl, unsubstituted, mono- or di-substituted independently by halogen, lower alkyl or (CH_2)n-$C(O)OR^{21}$, wherein n is 0, 1 or 2 and R^{21} is lower alkyl.

5. A compound according to claim 1, wherein

R^4 is -$C(O)NHR^{16}$;

R^{16} is hydrogen, lower alkyl, lower alkenyl, hydroxy lower alkyl, -(CH_2)n-$COOR^{18}$, -CO-(CH_2)n-$COOR^{19}$;

n is 0, 1, 2. 3 or 4;

R^{18} and R^{19} are independently hydrogen or lower alkyl,

and its pharmaceutically acceptable salts thereof.

6. A compound according to any of claims 1 or 5, wherein R^4 is -$C(0)NHR^{16}$, and R^{16} is lower alkyl or lower alkenyl.

7. A compound according to any of claims 1 to 6, wherein R^1 is hydrogen, halo, nitro or cyano.

8. A compound according to any of claims 1 to 7, wherein R^1 is hydrogen or halo.

9. A compound according to any of claims 1 to 8, wherein R^2 is hydrogen, halo, nitro, cyano, sulfonamido, lower alkyl, $-OR^5$, $-COOR^5$, perfluoro- lower alkyl, lower alkyl sulfonyl; or
R^2 can be R^{10}-[(CH_2)y-W]z-, where
W is oxygen, sulfur, -SO-, or $-SO_2$-, and
R^{10} is a heteroaromatic ring, connected by a ring carbon atom, which contains from 5 to 6 ring members with from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur or nitrogen, or
aryl containing 6 or 10 ring carbon atoms, or
aryl containing 6 ring carbon atoms fused with a heteroaromatic ring containing 5 or 6 ring members with 1 or 2 heteroatoms in the ring being selected from the group consisting of nitrogen, oxygen or sulfur, or
a saturated 5- or 6-membered cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, or
a cycloalkyl ring having 5 or 6 carbon atoms, or
$-NR^{11}R^{12}$, with R^{11} and R^{12} being independently hydrogen or lower alkyl;
y is independently 0,1,2,3 or 4; z is independently 0,1; or
R^2 can be R^{13}-(CH_2)t-U-, with
U is -NHCO-, -CONH, $-NHSO_2$-, $-SO_2NH$- and
R^{13} in the same meaning of R^{10} and
perfluoro-lower alkyl, lower alkyl, lower alkoxycarbonyl or
$-NR^{14}R^{15}$, R^{14} and R^{15} are independently hydrogen or lower alkyl; or together with the nitrogen atom to which they are attached form a five or six-membered heteroaromatic ring containing from 1 to 3 heteroatoms selected from sulfur, oxygen or nitrogen;
t is an integer from 0 to 4.

10. A compound according to any of claims 1 to 9, wherein R^2 is halo, lower alkyl sulfonyl or R^{10}-[(CH_2)y-W]z-.

11. A compound according to any of claims 1 to 10, wherein R^2 is sulfonylmethyl or R^{10}-[(CH_2)y-W]z- where W is SO_2.

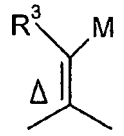
12. A compound according to any of claims 1 to 11. wherein V is cyclopentyl, cyclohexyl or cycloheptyl.

13. A compound according to any of claims 1 to12, wherein V is cyclopentyl.

14. A compound according to any of claims 1 to 11, wherein R^3 is isopropyl or n-propyl.

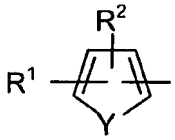
15. A compound according to any of claims 1 to 11, wherein R^3 is isobutyl.

16. A compound according to any of claims 1 to 15, wherein Z is



17. A compound according to claim 16, wherein M is hydrogen, fluorine or methyl.

18. A compound according to any of claims 1 to 17, wherein A is



19. A compound according to any of claims 1 to 18, wherein Y is sulfur.

20. The use of the compounds according to any of claims 1 to 19, or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of type II diabetes.

21. A pharmaceutical composition comprising a compound of any of claims 1 to 19, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

22. The use of a compound according to any of claims 1 to 19, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of type II diabetes.

23. A method for the prophylactic or therapeutic treatment of type II diabetes, which comprises administring a compound of any of claims 1 to 19, or a pharmaceutically acceptable salt thereof, to a human being or animal in need thereof.

24. A pharmaceutical composition for treating type II diabetes containing as an active ingredient a compound of any of claims 1 to 19, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/37089

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 A61K31/427 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/12189 A (BRASCA MARIA GRABRIELLA ; TRAQUANDI GABRIELLA (IT); ORSINI PAOLO (IT);) 22 February 2001 (2001-02-22) claim 1	1
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 2004	15/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Baston, E

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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/08209 A (HOFFMANN LA ROCHE) 31 January 2002 (2002-01-31) *Examples, claim1*	1-24
Y	WO 01/85707 A (HOFFMANN LA ROCHE) 15 November 2001 (2001-11-15) *Examples, claim 1*	1-24
Y	WO 02/48106 A (HOFFMANN LA ROCHE) 20 June 2002 (2002-06-20) *Examples, claim1*	1-24
P,Y	WO 03/055482 A (NOVO NORDISK AS) 10 July 2003 (2003-07-10) claim 1	1-24
Y	WERMUTH ET AL: "The Practise of Medicinal Chemistry" PRACTICE OF MEDICINAL CHEMISTRY, XX, XX, 1996, pages 203-237, XP002190259 table 13.2	1-24
X	YOSHINA, S.; TANAKA,A.; USUI, T.: "Studies on heterocyclic compounds. XXIX. Synthesis of 2-'alpha-(N-substituted carbamoyl)-beta-(5-nitro-2-furyl)vinyl!furans and 2-'alpha-(N-substituted ureido)-beta-(5-nitro-2-furyl)vinyl!furans" YAKUGAKU ZASSHI, vol. 97, no. 9, 1977, pages 1007-1012, XP0009028638 examples III-11,III-15,III-16; table I	1

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